Ethical issues of clinical trials in children

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Abstract

Children should not be harmed by their participation in clinical trials, therefore should no clinical trials be performed? This is a view that needs to be balanced as clinical trials provide the evidence we need to allow children safe and effective prescribing of medicines. Therefore, is it unethical not to involve this population in research? The main push in the last decade has been to increase the number of medicines tested in the paediatric population. This culminated in the European Union ‘Paediatric Regulation’ in 2007 that meant that all new medicines, appropriate for use in children, must be researched in this population. The current challenge facing paediatricians involved in research is balancing harm, legislative requirements against the need for evidence based medicine. This review aims to debate some of the continuing ethical dilemmas, including practical considerations, faced by those involved with clinical trials in children.

Keywords clinical trials; ethics; paediatrics; research

Why do we need research in children?

Medical research involving children is essential for advancing child health and well being. In the past it was deemed acceptable to use adult research and extrapolate the results for use in children, but for a number of reasons this cannot be the case. Firstly, children are not small adults as the disease processes seen are different e.g. bronchiolitis in infants. Secondly, their physiological make up and their pharmacodynamic responses to drugs vary with age (and differ from adults). Therefore medicines need testing in all age groups from premature infants to adolescents, as child specific adverse drug reactions are seen. Finally therapies used for adult, such as tablets, are not well tolerated particularly in younger children because they are difficult to administer or unpalatable.

A large number of medications in all clinical settings in paediatrics are either unlicensed or used in an off label manner. One of the aims of the Paediatric Regulation is to stimulate research in these medicines. Companies will benefit from 10 years of data protection as a reward for the development of new indication in children or formulations appropriate for children of all ages. This legislation however has failed to produce good results, with only one medication (buccal midazolam) being approved so far.

We do however need to take care in recommending research on all of the medicines used in children, as for many there is good clinical evidence of their safety and efficacy. A good example of this is the recent change to the labelling of amoxicillin in children to update the licenced recommendations for dose. Concern has previously been raised that the American legislation resulted in more paediatric clinical trials of medicines widely used in adults e.g. studies of antihypertensives. Therefore ethically, further clinical studies need to focus on medications relevant to children’s clinical needs where there is limited evidence of efficacy.

Risk versus benefit

One of the hardest ethical challenges of paediatric research is the balancing of benefit from a study against the harm and risks. Risk assessment is a crucial step in evaluating a protocol and conducting a clinical trial. Risk is defined as potential harm (real or theoretical) or potential consequence of an action. It may be physical, psychological, or social, and may be immediate or delayed. The risks of any clinical trial should be considered in conjunction with the severity of the condition or diseases to be studied, the age of the child and the risks and benefits of alternative treatments.

The EU ethical guidance that supports the Paediatric Regulation defines three levels of risk, as seen in Table 1, and practical examples have been included for each group. Minimal risk is defined as the probability of harm or discomfort not greater than that ordinarily encountered in daily life or during routine tests.

The way we describe risk has a huge impact on families understanding and acceptance of research proposals. An interview study looked at parents and children views on facing research risks; children aged 7—14 years and their parents with 81 child —parent pairs were interviewed. For a theoretical study that had no benefit but a one in a million chance of death, only 40% of children and 19% of parents were willing to participate. Interestingly when the risk was described as “the same risks as riding

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Table 1

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in a car” (a single car trip across town during a rush hour poses approximately a 1 in 100,000 chance of death in a child). 89% of children and 93% of parents agreed. Further research is needed so that we can establish both child and parental understanding of the risks involved in clinical research.

Benefit can be defined as progress in treatment, diagnosis or prevention for the child or the group of children affected. This may be an increased efficacy, safety of a drug or an alternative to existing treatment. This may include a change to the administration, dosing frequency or duration of a drug but may involve reduction in medication errors or production of a more age appropriate formulation.

The current EU guidance allows the following levels of risk in balance with benefit in trials in children:

- minimal risk with benefit for the individual or benefit of the group.
- minor increase over minimal risk, with benefit to individual or group and with the benefit to risk balance being at least as favourable as alternative approaches.
- greater than minor increase over minimal risk with benefit for the individual that is especially favourable in relation to available alternative approaches for the individual’s condition.

It is our ethics committees that are challenged with reviewing and assessing the risk and benefit of these research protocols. Shal et al. conducted a telephone interview of 188 heads of Institution Review Boards (IRB) in the USA and asked them to categorise the risk level and direct benefits of paediatric research procedures. They found the results to be variable, 27% of IRB chairpersons categorised allergy skin testing as too risky for IRB approval without a prospect of direct benefit to the participating children, while 66% deemed such testing safe enough for IRB approval without a prospect of direct benefit. One of the ongoing ethical challenges in our vulnerable population is therefore this ongoing balance of risk versus benefit.

Risk monitoring

As the level of risk may evolve over time during any research project or with expanding knowledge, risk should be continually monitored and pre specified within the protocol. The EU guidance recommends the use of a Data and Safety Monitoring Board (DSMB) and should include paediatric specialists. In a study of short duration or a single dose pharmacokinetic study a DSMB may not be necessary, this however should always be justified. A literature review over 7 years (1996–2002) of randomised control trials in children showed that only 13% of trials had a DSMB.

Informed consent

Consent is defined as the voluntary agreement, to participate in research based on adequate knowledge and understanding of relevant information. As the child (minor) is unable to provide legally binding consent, and his/her assent does not have sufficient authority to authorise research, the parent(s)/legal representative are required to provide consent on the behalf of the child for participation. It is important to understand that consent is an ongoing process and should be maintained throughout the study period which could be done regularly through consultations, and should be well documented.

Separate information sheets should be produced for adults and children including separate consent and assent forms. These should be written in appropriate wording and language and reviewed by families and children. Early review of study information and protocols should take place by children and their parents to enhance acceptability of the study, such as the number of visits, timing of appointments and invasiveness of proposed procedures. The CRN Young Person’s Advisory Groups, with six around the UK, are an excellent resource in helping with this process.

The question on who takes consent is an ongoing ethical debate. There is concern that there may be conflict of interest when the same person acts as both a child’s treating physician and as the investigator recruiting the child to a study. This was investigated in a qualitative study of almost 60 families who had been approached about one of four different trials, where some of the trials had used a dual-role clinician—investigator ‘model’ during recruitment while others maintained role separation by using clinicians who were uninvolved in the child’s care to conduct the trial approach. They showed that parents tended to emphasise the benefit of whichever ‘model’ they had encountered. This perhaps indicates that parents do not have strong preferences either way, however, patient minors seemed to prefer interacting with practitioners whom they knew.

It is important that consent is given free from coercion. Payment in research around the world in adults is common but controversial. Payment can enable participation in research without disadvantage and boost recruitment, but it must not lead participants to ignore or significantly undervalue risk. This can have an added complexity when the inducement is offer to the parent and not the child taking the risk. It has been found that when inducements have been offered this can influence parental reasons for consent, with a positive correlation between the importance of free medication as a reason for consent and lower income families. The EU Paediatric Regulation states that there must be no financial inducement to enrol a child in a trial, with exception of compensation for time and expenses. The ethical balance is therefore a fine line, which should allow appropriate compensation but not lead families to ignore, misunderstand or significantly undervalue serious risks.

Assent

We both have an ethical and legal obligation, to obtain a child’s permission for their participation in research. The US Code of Federal Regulations defines assent as a child’s affirmative agreement to participate in research. Mere failure to object should not, in the absence of affirmative agreement, be construed as assent. Allowing children to be part of the decision process respects their evolving maturity. Time should be taken for this process and should be done along side obtaining consent from the parents. Research has shown that children from the age of 9 years can understand the risks and benefits of research. Across different countries, assent is widely but not globally recognised. The American Academy of Pediatrics endorses 7 years as a minimum age for assent, whilst different European states vary between 7 and 16 years.

Evaluation of whether a child can assent should not be based on chronological age alone but should depend on other factors
such as intelligence, developmental stage, diagnosis and life experience. A key message from the Nuffield Bioethics Foundation report (2015) (Children and clinical research: ethical issues) was when children and young people have sufficient maturity and understanding, but are not yet treated legally as adults, professionals should seek consent both from children and from their parents.

Practical difficulties

For those involved in research in children a number of different challenges especially practical methodological difficulties can be faced. The next few paragraphs focus on the regular problems faced by paediatric researchers.

Pharmacokinetic studies

Design methods need to be optimised to allow for the smallest number of patients to be recruited to give a statistically and clinically significant result. A typical pharmacokinetic (PK) study in adults will involve around 15 blood samples taken following the administration of the drug of interest. This methodology cannot be ethically used to children. An example of this is a study in 1997 looking at the pharmacokinetics and efficacy of cyclosporine A in paediatric transplant patients. This study involved 13 blood samples of 5 mls during one dose interval in 18 patients. The invasiveness of this protocol was felt to be unethical due to the large number and volume of samples. Population pharmacokinetics is a useful technique in paediatrics using a smaller number of blood samples from each patient with an increased number of patients pooling their data. In fact this technique was used by the same group quoted above in subsequent years to further investigate cyclosporine A dosing regimes.

Venepuncture and blood sampling

Children do not like venepuncture, therefore alternative methods to other blood sampling should be considered wherever possible. Studies have used saliva, urine or breath testing but it has been difficult to achieve reproducible results using these methods. However, when blood and tissue assays are required micro volumes or micro-assays should be used and indwelling catheters for repeated blood sampling. If a child is undergoing blood sampling, or other painful procedures for research, it is essential to think about appropriate anaesthesia. It is also important to think about timing of samples and to coincide with other therapeutic sampling. Distraction techniques should be used.

It is important that studies involving children have specialist input from those experienced in paediatric research with additional input from families, and if possible the age range of children that are going to be studied.

Placebo use

Historically medicines have been tested against placebo. Now that treatments exist for most conditions, clinical trials of a new medicine should be against an active comparator and current treatments should not be ceased. A study in younger children aged 4–8 years compared the safety and efficacy of nebulised budesonide at three strengths to placebo. 60% enrolled in the study were on asthma preventative steroid inhaler treatment which was stopped for those in the placebo group. A large proportion in the placebo group dropped out due to asthma exacerbations and a higher number received of courses of oral/parental steroids for exacerbations. This study would have been ethically sound if comparison between budesonide groups (or the current standard treatment) had been undertaken rather than comparison to placebo.

Placebo trials can be undertaken in certain circumstances, for example if the paediatric evidence for any particular treatment is lacking or in studies looking at palatability of medicines.

Drug formulations

Age appropriate formulations should be used to avoid risk of adverse reactions (for example choking on tablets) or dosing errors. If paediatric formulations are available then these should be used and described in the study protocol and future publications. The EU Paediatric Regulation has promoted the importance of the development of appropriate formulations for children from the beginning of drug development, making this a requirement for the Paediatric Investigation Plan needed for licencing.

Special population considerations

Emergency setting

The only exception for the requirement of consent before research can take place is emergency medical care. If a research project has been approved by a research ethics committee then it is ethical in occasions of extreme urgency, without parental consent. Both consent, and if appropriate assent, should be sought soon as after the emergency period as deemed possible. An example of such a study would be Buccal Midazolam versus Rectal Diazepam for acute epileptic seizures in children. Both of these routes were being used in clinical practice so institutions randomised on alternative weeks to each treatment. Consent was then taken to include the child’s data once they had recovered from their seizure. Research in this environment is ethically challenging as we are most often dealing with life threatening situations. Therefore we need to balance the need for evidence based care with needs of parents and children in this stressful situation. More research is needed in this field.

Neonates

Neonates whether preterm or term are a vulnerable population group. It can be difficult to get consent given the stress of the situation especially those treatments that need to be started straight after premature birth. Using antenatal counselling before birth has been suggested by parents as a way to improve the consent process. Another problem faced in neonatal research is their limited blood volume. Neonates often become anaemic either due to their concurrent illnesses but also because of regular clinical blood sampling. EU guidance recommends that for research the maximum volume which can be taken is 3% of the total blood volume over 4 weeks. Total blood volume equals 80 mls per kg body weight and therefore 3% equates to 2.4 ml blood per kg body weight.

Adolescents

The use of this group to conduct research can be a challenge. For research purposes, adolescences are incorporated into the paediatric group requiring parental consent. However in other areas
of life they have the capacity to make adult decisions. It is therefore paramount to obtain assent in adolescents involved in research with this being respected. Another issue is that of confidentiality especially in research involving issues around illicit drug use, sexuality and violence. Assent in these areas is even more critical and confidentiality of information needs to be explained to the teenager during the assent process. Finally it is important to remember that in some studies, adolescents may turn of age during their participation in research. Informed consent from the individual is needed for them to continue within the research as soon as possible.

Healthy children
The EU guidance stipulates that research on healthy children should not be performed. Exceptions to this include palatability research such as swill and spit tasting for new flavoured medicines and vaccine trials. Prevention or vaccine trials will include healthy children but as they could potentially benefit that child and a larger population, they are therefore acceptable to undertake.

International differences
It is important that in multinational studies separate ethical reviews are performed and accepted in each of the participating countries. This important as different countries may have variations in regulations and patient information will need to be presented in a culturally appropriate manner. For example, in the United States, studies can be approved that do not offer a prospect of direct benefit to healthy children when they pose either only minimal risk or minor increase over minimal risk.

Conclusion
Since the development of both the US and EU Paediatric Regulations, there has been a dramatic increase in the amount of paediatric research being undertaken in both new and established medications. This is a huge step forward but the focus needs to continue in areas where clinical knowledge is lacking or insufficient. Research in children needs to be safe and ethical, which can be challenging. The emphasis needs to be on using the correct methodology and study design, with input from those with expert knowledge and the involvement of patients and their families

Table 1.

Funding
None.

FURTHER READING


Practice points
- Clinical trials need to focus on medicines where efficacy, dosage or formulations are lacking
- Risks should be expressed in a way parents can understand.
- DSMB should be considered for all paediatric clinical trials.
- Consent is an ongoing process
- Assent should be considered for all children where developmentally appropriate (from 7 years) and a joint consent process should be considered for older children
- Blood tests should be timed to coincide with therapeutic sampling and analgesia should always be used
- Placebo should only be used when no clinical treatment for comparison exists
- Parents and children should be involved in the design of studies and writing of information for participants